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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/729,658	12/04/2000	Jonathan Zonana	6005-55924	3101

7590 02/14/2005

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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,658	ZONANA ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,22-26,41,42 and 51-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,22-26,41,42 and 51-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 11/22/04. Claims 5-21, 27-40 and 43-58 have been cancelled. Claims 65-71 have been added. Claims 2, 4 and 42 have been amended. Claims 1-4, 22-26, 41-42 and 59-71 are pending in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein that were not necessitated by applicants' amendment and therefore, this action is final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 68-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment. This is a new matter rejection.**

The limitation that the method of increasing hair follicle development, tooth development or sweat gland development comprises administration of an EDA1-II that is the C-terminal 240 or 211 amino acids or includes an amino acid substitution at position E294 such as E294V,

E294L, E294A or E294T has been added to claim. Applicant has indicated that support for these limitations are found on page 21, lines 14-16 and 21-22 and page 22 lines 12-15 and figure 4. These sections teach that within the C-terminal 211 amino acids, a single conservative substitution between Tabby proteins and EDA1-II can be found and that biologically active domains of EDA1-II can be found in the C-terminal 240 amino acids such as residues 133-391, 153-391 and 239-391 and that the second amino acid (E) of aligned sequences of the TNF family members can be substituted with V, L, A or T. It is believed that the second amino acids refer to the amino acid that is second in figure 4. These passages and the remainder of the specification do not disclose that the method of increasing EDA1-II can be or should be performed using EDA1-II comprising the C-terminal 240 or 211 amino acids or in which E294 has been substituted. The examiner has been unable to find literal support in the originally filed specification for a method of administering an amount of EDA1-II that is the C-terminal 240 or 211 amino acids or in which E294 has been substituted to a tissue sufficient to promote either hair follicle development, tooth development or sweat gland development. Therefore, the limitation of adding "administration of an EDA1-II that is the C-terminal 240 or 211 amino acids or includes an amino acid substitution at position E294 such as E294V, E294L, E294A or E294T" is impermissible NEW MATTER.

Claims 64, 70 and 71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. **This rejection is maintained for reasons of record in the office action mailed 5/19/04 and restated below. Upon reconsideration, the rejection of claims 59-63 has been dropped. The rejection has been extended to newly added claims 70 and 71.**

The instant invention is drawn to a method of increasing hair follicle development, tooth development or sweat gland development that is dependent on increasing EDA1-II protein activity. In claims 64, 70 and 71 applicants recite a genus of amino acid substitution mutants of SEQ ID NO: 2 that can be administered to increase EDA1-II activity.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant case, applicants disclose that SEQ ID NO: 2 corresponds to the amino acid sequence of EDA1-II, a splice variant of EDA1. EDA1-II isolated from ectodermal diseases such as XLHED and HED or alopecia contains multiple mutations in exons 3-9. Accordingly, applicants have proposed that an increase of EDA1-II activity by administration of the recited EDA1-II proteins would lead to the development of hair follicles, teeth and sweat glands. Claim 64 is directed to mutants of SEQ ID NO: 2 with 1-10 amino acid substitutions. Claims 70 and 71 are directed to mutants of SEQ ID NO: 2 with substitutions of V, L, A or T at E294.

The specification teaches that the 240 or 211 C-terminal comprise the biologically active portion of EDA1-II and that within the C-terminal 211 amino acids, a single conservative

substitution between Tabby proteins and EDA1-II at E294 can be found. An alignment of the TNF family demonstrates that the second amino acid (E) of EDA1-II is substituted in the aligned sequences of the TNF family members with V, L, A or T (page 21, lines 14-16 and 21-22 and page 22 lines 12-15 and figure 4). However, it is not clear what role these other members of the TNF family play in tooth, hair and sweat gland development and therefore, it is unclear that mutations in SEQ IDNO;2 can be anticipated to result in biologically active fragments based solely on the observation that the amino acids are different in related peptides particularly given the lack of involvement of the related peptides in ectodermal disease. No mutants of SEQ ID NO: 2 are demonstrated as capable of increasing hair follicle development, tooth development or sweat gland development. Neither applicant nor the prior art provide a correlation between the structure of the recited mutated sequences and the ability to induce development of hair follicles, teeth or sweat glands. Given the diversity and large size of the genus of mutations of SEQ ID NO: 2, and the inability to determine which will also have the recited ability, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of the broadly claimed genus.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 5-7 of the amendment filed 11/22/04. Applicants argue the following. The specification provides a detailed correlation between the structure of EDA1-II and the ability to induce development of ectodermal structures such as the regions and amino acids most likely to have the desired

biological activity. Specifically, by comparison of the EDA1-II and Tabby protein sequences, the central beta sheet of the TNF family of proteins and an analysis of known mutations in ectodermal disease (shown in table 1) has been said to identify, amino acids that can and can't be substituted without loss of substantial biological activity. In summary, those regions that can be substituted without substantial loss can be identified as amino acids 1-180 and sub regions thereof because they are less conserved between Tabby and Eda1-II. Mutations identified in patients with ectodermal disease are correlated with particular domains, which are localized to the C-terminus. Therefore, N-terminal amino acids would tolerate substitutions more than the C-terminus. Those regions that can be substituted without substantial loss can be identified an alignment of the central beta sheet between TNF family members). the importance of a single conservative amino acid substitution in the terminal 211 amino acids and therefore this region is important in protein function. As well, incorporation of the mutations that occur in patients with ectodermal disease would not likely lead to simulation of ectodermal structures. Applicants conclude that coupled with the available tests for EDA1-II activity to stimulate hair tooth and sweat gland growth (see example 19), applicants have provided adequate written description for the recited peptides.

Applicants' arguments filed 11/22/04 have been fully considered but they are not persuasive. The specification is directed to a splice variant of EDA1, EDA1-II, isolated from ectodermal diseases such as XLHED and HED or alopecia and that contains multiple mutations in exons 3-9. These fragments encompass a broad genus of proteins comprising 1-10 amino acid substitutions or an E294 amino acid substitution. While applicants have demonstrated that amino acid 2 of the central beta sheet comprises a non-conservative amino acid substitution E to

V, L, A or T. Based upon this observation, applicants have surmised that incorporation of these amino acids into the central beta sheet would have no effect on the biological activity of EDA1-II. However, it is not clear that these mutations would results in biologically active fragments simply because they are variant in other molecules. Applicants have provided no demonstrations as these mutations can be tolerated in EDA1-II or even in the related peptides. The occurrence of mutations in ectodermal disease teaches mutations that cannot be tolerated. However, this does not teach what mutations can be tolerated. The simple substitution of between 1-10 amino acids has the potential to generate a broad genus of peptides. The specification does not reduce to practice the ability to determine which peptides will also have biological activity and the ability to determine *a priori* whether a mutation or substitution will generate a functional fragment is highly unpredictable.

Claims 1-4, 22-26, 41-42 and 59-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in the office action mailed 5/19/04 and restated below. The rejection has been extended to newly added claims 65-71.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)).

Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a method of increasing hair follicle, tooth or sweat gland development by increasing EDA1-II activity.

2) **Scope of the invention**. The method recites administration of EDA1-II protein to the tissues to increase EDA1-II activity in humans suffering from ectodermal disease. This invention uses methods of protein therapeutics.

3) **Number of working examples and guidance**. Applicants teach several prophetic assays that are designed to identify agents that enhance EDA1-II activity on page 4, paragraph 0069. These include proposed *in vivo* methods that involve intradermal injection or topical application of the protein to the skin or tails of newborn tabby mice and detection of the induction of hair growth and injection of proteins into footpads of newborn tabby mice and monitoring of sweat gland development. Proposed *in vitro* assays include application of protein to dissected skin from mouse embryos and calculation of hair follicles that follow as well as application of truncated protein to an *in vitro* tooth organ culture system.

Once proteins that enhance EDA1-II activity have been identified, it is taught that the protein can be used in therapeutic applications. Specifically, it is disclosed that purified protein at concentrations ranging from 1 ng/ml to 1 g/ml is applied to the tails, bellies and areas behind the ears of newborn tabby mice, wild type mice and nude mice (see page 28, paragraph 0307) or is injected into footpads of newborn tabby mice (See page 28, paragraph 0309). Alternatively,

the protein can be applied to *in vitro* tooth cultures and the teeth introduced into humans or other organism (see page 28, paragraph 0308).

There is no actual introduction of the recited proteins *in vivo* in animal models or in humans. Nor are there proposed methods for the application of the recited methods for human use.

4) **State of Art**. The state of art for treatment of humans suffering from ectodermal dysplasia is not currently a high art. Cosmetic or functional correction is the only recourse patients have against this disease (see e.g. MedlinePlus medical encyclopedia). However, methods based on protein therapeutics for treatment of ectodermal dysplasia is a high art.

Torchilin and Lukyanov teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260).

Recently, permanent correction of ectodermal dysplasia in tabby mice has been reported (see Gaide and Schneider). In this study, application of EDA1 was conducted in pregnant tabby mice by serial intravenous injections of 400 μg of recombinant EDA1 (in 2mg/ml PBS) following two different dose schedules. Newborn mice received a single intradermal injection at the same dose (see Gaide and Schneider, bridging paragraph page 617-618). Formation of hair, teeth and sweat glands were induced in the newborn mice.

5) **Unpredictability of the art**. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice

experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Deiry, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies.

Furthermore, any successes in the published document by Gaide and Schneider cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of the reference. The teachings of the instant invention differ from that of Gaide and Schneider. Neither the specification nor the teachings of Gaide and Schneider provide adequate guidance for the application of EDA1-II to humans for the treatment of ectodermal dysplasia. Problems with protein therapeutics identified in the art are not addressed by the methods of the instant invention nor the prior art. Therefore, neither the specification nor art teach one how to treat ectodermal dysplasia by introduction of EDA1-II as neither the specification nor the prior art provide dosages of EDA1-II to administer to patients, schedule of treatments, specific modes of administration of EDA1-II to humans suffering from ectodermal disease is provided.

6) **Summary**. The invention recites a method of treating ectodermal disease by the administration of EDA1-II protein to a subject using gene therapy. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of: undue experimentation would be required to practice the claimed methods with reasonable expectation

of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of enablement on pages 7-14 of the amendment filed 11/22/04. 1) In response to the wands analysis of the guidance in the specification, applicants argue that clear teaching is provided throughout the application for administration of EDA1-II protein to treat ectodermal disorders in humans. Specifically, applicants point to sections of the specification that indicates that treatment is directed to humans. For example, the specification provides four references for protein delivery to hair follicles and protein delivery to human skin including the scalp are well known. Example 19 discloses methods to increase tooth growth that are not limited to mice. EDA1-II can be administered to an in vitro tooth organ culture system and then subsequently introduced into humans or other organisms. While applicants disclose that EDA1-II stimulates sweat pad development in mice by injection into footpads, injection into the skill can be performed by means of injection of EDA1-II into humans. (see page 72, lines 21-23). Applicants reference several other sections that teach how to administer EDA1-II to human subjects. For example, particular modes of administration for increasing hair follicle, tooth or sweat gland development are provided on page 17, lines 12-20 and 72, line 18-37. 2) In response to the Wand's analysis of the unpredictability of the art, applicants argue that the EDA1-II protein as demonstrated by Gaide and Schneider does not appear to be rapidly eliminated from circulation.

Furthermore, following topical administration, the protein would not be expected to face problems of rapid elimination. As well, applicants reference Mrsny that teaches that potential protein therapeutics act at the site where administered and therefore administration of EDA1-II to an area of treatment means it is likely to act in that area. 3) In response to the Wand's analysis of the unpredictability of the art, applicants traverse that the success of animal models such as from Gaide and Schneider cannot be considered as evidence of success of treatment. Firstly, the Tabby mouse is the accepted mouse model for the human disease ectodermal phenotypes as Gaide and Schneider et al that teaches the mice with Tabby phenotype share many symptoms with human XLHED patients and because other groups of skill in the art have recognized that the Tabby mouse is the mouse homolog of the human EDA1-II gene. Secondly, human data is not required to demonstrate success. Thirdly, teachings of Gaide and Schneider can be extrapolated back to the instant specification as relates to the protein injected, doses and modes of administration. Finally, the application does disclose dosages, schedules and specific modes of administration (see collectively page 15, lines 10-12, page 50, line 27-34, page 51, lines 6-7, 20 and 31, page 72, line 21-37.

Applicants' arguments filed 11/22/04 have been fully considered but they are not persuasive. As regards arguments based upon the guidance in the specification, applicants have only demonstrated that the specification contemplates administration of EDA1-II to humans for an increase of hair follicle, tooth and sweat gland development. However, the specification does not teach adequate and specific guidance for the administration of EDA1-II to humans for treatment of ectodermal disease or alternatively *in vitro* or *in vivo* models. Human models are not required nor were they requested. The guidance applicants refer to on page 15, 50 and 51

provide exemplary doses of protein administration in prophetic disclosure as to amounts that would be therapeutically effective. The guidance on page 51 even states that the protein can be applied at a concentration of 1ng/ml to 1g/ml, which spans a 1,000,000-fold-dosage amount. The guidance on page 17 describes % identity of EDA1-II proteins required for enhancing EDA1-II activity in cells or tissues. These passages clearly demonstrate that the guidance in the specification is prophetic and simply provides general guidance on acceptable means of administering in a therapeutic setting and is not specifically directed toward application of EDA1-II. It is not clear which of the many means of administration are actually contemplated by applicants or which would adequately deliver EDA1-II to the targeted structures for hair follicle, tooth or sweat gland development.

Given the broad ranges it is not surprising several of the instantly proposed administration routes overlap with those provided by Gaide and Schneider. However, considered in closer detail, the teachings of the instant invention differ dramatically from that of Gaide and Schneider. Gaide and Schneider teach administration of recombinant EDA1-II and the Fc domain of IgG1 that is intravenously injected into pregnant Tabby mice intraperitoneally or intravenously into newborn mice for the sole purpose of altering the phenotype of the fetal mice. None of the treatments were successful in altering any of the Tabby phenotypes in the adult mice. Injections at gestational day 11, 13 and 15 at 400 um per injection, called E11 reversed most of the Tabby characteristics except teeth and hair growth were not completely wild type. Other treatments included gestational treatment at day 15 and 17 (E15) as well as injection of newborn mice at day 2, 3, 5, 9 (D2, D3, D5, D9). The subsequent treatments had decreasing effects on the Tabby phenotype. Newborn injections only consistently corrected sweat gland

development. However, teeth and hair were either not or were poorly corrected (see e.g. table 1). Applicants have not proposed injection of pregnant Tabby mice with a recombinant EDA1-II that has been engineered to pass the placental barrier. Furthermore, applicants have not indicated that the EDA1-II would be used to reverse phenotype via genetic routes. Rather the instant specification has indicated that the effects of EDA1-II would be demonstrated in the actual patient injected. Following this approach, the success of treatment in increasing hair follicle, tooth and sweat gland development would be expected to be insufficient in treating each of these disorders as demonstrated by the increasing failure of treatments to reverse the ectodermal phenotype in the newborn mice s demonstrated by Gaide and Schneider. Therefore, means of administration of protein for the treatment of each of these disorders using the guidance provided in the specification is highly unpredictable.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 2, 2005

GERRY LEFFERS
PRIMARY EXAMINER